Use of Intra-operative Steroids Reduces Major Respiratory Complications After Pneumonectomy

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Background

Pneumonectomy
- Associated with high risk of post-operative respiratory complications
- Post-pneumonectomy pulmonary edema (PPE)
- Incidence: 4–16% of pneumonectomies
- Mortality rate of 50% to 75%
- Likely a form of ARDS
- Pathophysiology poorly understood but postulated to involve inflammatory mediators, reactive oxygen species, peri-operative fluid overload
- Few preventive strategies have been used other than fluid restriction
- Intra-operative methylprednisolone has been suggested to reduce PPE
- Limitations: small sample size, non-adjusted analyses

Objective

Primary
- To determine if use of intra-operative steroids reduces incidence of major respiratory complications in adult patients undergoing elective pneumonectomy

Secondary
- To assess predictors of major respiratory complications after elective pneumonectomy

Methods

Retrospective cohort study using prospectively-collected data

Study population:
- Adults that underwent elective pneumonectomy between 2003 & 2011
- Single tertiary care centre in Canada by 3 thoracic surgeons

Exposure
- All types of steroids were considered
- Bio-equivalent steroid doses were calculated & categorized as:
  - None
  - Low (up to 200mg hydrocortisone-equivalent)
  - High greater than 200mg hydrocortisone-equivalent

Outcomes
- Primary Outcome:
  - Composite outcome of post-operative major respiratory complications:
    - In-hospital mortality
    - Respiratory failure (need for mechanical ventilation)
    - Acute Respiratory Distress Syndrome (Berlin criteria)
  - Post-pneumonectomy pulmonary edema (PPE) was considered as equivalent to ARDS if met Berlin criteria
- Secondary Outcomes:
  - Bronchopleural fistula
  - Median length of stay
  - Median number of ventilated days

Analysis
- Univariate analysis
- Independent samples t-test
- Fisher’s exact
- Multivariate logistic regression using:
  - Pre-operative lung function (FEV1 and DLCO/VA on pulmonary function tests)
  - Pre-operative co-morbidities
  - Pre-operative fluid balance
  - Pre-operative chemotherapy
  - Era of treatment

Results

- 140 pneumonectomies performed
- Intra-operative steroids used in 32 (23%)
- Steroids used were:
  - Hydrocortisone (dose range: 100-250mg)
  - Methylprednisolone (125mg)
  - Dexamethasone (dose range: 1-10mg)
- Higher bioequivalent doses of steroids were usually achieved with methylprednisolone

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Steroids (n=32)</th>
<th>No Steroids (n=108)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years [SD]</td>
<td>81.25 (15.14)</td>
<td>64.84 (10.12)</td>
</tr>
<tr>
<td>% male [n]</td>
<td>31.2% (9)</td>
<td>44.0% (48)</td>
</tr>
<tr>
<td>% right pneumonectomy [n]</td>
<td>37.5% (12)</td>
<td>51.8% (56)</td>
</tr>
<tr>
<td>Mean BMI in kg/m² [SD]</td>
<td>25.72 (4.07)</td>
<td>26.82 (4.85)</td>
</tr>
<tr>
<td>ASA class</td>
<td>ASA I: 0 (0)</td>
<td>ASA II: 0 (0)</td>
</tr>
<tr>
<td>ASA II 46.9% [15]</td>
<td>ASA III: 58.6% (56)</td>
<td>ASA IV: 53.1% (17)</td>
</tr>
</tbody>
</table>

Mean FEV1 % pred [SD] 76.18 (15.12) 76.25 (20.49) 0.99
Mean DLCO % pred [SD] 69.50 (17.42) 68.76 (23.26) 0.89
Mean % of packed cells [SD] 38.31 (20.83) 36.83 (22.48) 0.77
% Pre-operative chemoradiation [n] 31.2% (10) 18.5% (20) 0.14
Mean daily fluid balance in ml [SD] 643.46 (572.19) 667.82 (615.30) 0.83
Era of treatment 2003-2007: 18.0% (6) 62.5% (27) 2008-2011: 81.2% (26) 37.5% (12)

Although there was significantly more use of steroids in later time period, there was no actual differences in the outcomes of interest (i.e. in-hospital mortality, respiratory failure and ARDS) between time periods. This was further confirmed on multivariable analysis.

Table 2: Outcomes (univariate comparison)

<table>
<thead>
<tr>
<th>Steroids (n=32)</th>
<th>No Steroids (n=108)</th>
<th>p</th>
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<tbody>
<tr>
<td>% In-hospital mortality [n]</td>
<td>6.2% (2)</td>
<td>5.7% (6)</td>
</tr>
<tr>
<td>% Respiratory failure [n]</td>
<td>18.8% (6)</td>
<td>21.7% (23)</td>
</tr>
<tr>
<td>% ARDS (mild or severe) [n]</td>
<td>12.5% (4)</td>
<td>13.8% (15)</td>
</tr>
<tr>
<td>% experiencing composite outcome [n]</td>
<td>28.1% (9)</td>
<td>35.6% (38)</td>
</tr>
<tr>
<td>% Bronchopleural fistula [n]</td>
<td>0 (0)</td>
<td>2.8% (3)</td>
</tr>
<tr>
<td>Median length of stay in days (range)</td>
<td>7 (73)</td>
<td>7 (84)</td>
</tr>
<tr>
<td>Median length of stay in days (range)</td>
<td>0 (0)</td>
<td>0.00 (0)</td>
</tr>
</tbody>
</table>

- The rate of major respiratory complications overall was 34% (n=47).
- After controlling for confounders, independent predictors of reduced major respiratory complications were:
  - **Use of higher-dose steroids intra-operatively**
    - OR=0.07 (95%CI: 0.006-0.84, p=0.04)
  - Use of LOWER Dose steroids was not associated with significantly lower respiratory complications when compared with NO steroids
    - OR=0.16 (95%CI: 0.02-1.93, p=0.14)
  - Having a left rather than a right pneumonectomy
    - OR=0.33 (95%CI: 0.15-0.75, p=0.008)

Conclusions

- The use of higher-dose steroids intra-operatively during pneumonectomy is associated with decreased major respiratory complications when compared to no steroid use.
- It is not associated with increased risk of bronchopleural fistulae
- Sidedness was the only other independent factor in influencing rate of major respiratory outcomes
- Right pneumonectomy is higher risk

Strengths
- Largest study of its kind to date
- Multivariate logistic regression was used to adjust for confounders

Limitations of this study include:
- Non-standardized administration time of steroids
- Non-standardized dosing of steroids
- This study provides stronger evidence that there may be a role for intra-operative steroids in pneumonectomy
  - Provides impetus for further studies in this field

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